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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,716	01/11/2002	John Langenfeld	270/070	1276

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 10/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,716	LANGENFELD, JOHN	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 May 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed August 10, 2005 is acknowledged and has been entered. Claims 2-4, 9, 11, 12, 14-16, 20-25, 27, 29, and 31-64 have been canceled. Claims 1, 6, 18, and 19 have been amended.

2. Claims 1, 6, and 17-19 are pending in the application and are currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, Applicant's amendment and/or arguments filed August 10, 2005 have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed April 25, 2005.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

6. The rejection of claims 1 and 17-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At pages 15-18 of the amendment filed August 10, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that, at the time of filing, the structure and function of polypeptides that antagonize the activity of BMP-2 were well known in the art. In reply, the claims are directed to a genus of polypeptides that bind specifically to a bone morphogenetic protein-2 (BMP-2) so that BMP-2 receptor activation is prevented. As explained in the preceding Office action, while there were known inhibitors of BMP-2, the structures and functions of these molecules are very dissimilar. The written description provision set forth under 35 U.S.C. § 112, first paragraph, requires that the claimed invention be described in such a way as to reasonably convey to the skilled artisan that Applicant had possession of that invention at the time the application was filed. As further explained in the preceding Office action, the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, while possession may be shown in a variety of ways, because the claims are directed to a genus of structurally and functionally disparate molecules that merely share the common ability to bind specifically to BMP-2 and prevent BMP-2 activation, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species. This may be achieved, for example, by reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, there is no factual evidence in the specification of an actual reduction to practice, as only a few members of the genus have been described; and Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete. Furthermore, Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed. Because the members of the genus, which have been described, have not been described as

sharing, and do not appear to share any distinguishing identifying features, the skilled artisan could not immediately envision, recognize or distinguish members of the genus of polypeptides that bind specifically to BMP-2 and prevent activation of its receptor. In other words, while the members of the genus have been described as sharing a particular functional property, there is no disclosed correlation of this activity and a substantial or particularly identifying structural feature also shared by the members of the genus, which might permit the skilled artisan to instantly envision, recognize or distinguish members of the genus from other polypeptides. What structural feature is it that is disclosed in the specification, which is shared by members of the genus and confers their common ability to bind to BMP-2 and thereby prevent the activation of the receptor, so as to allegedly permit the skilled artisan to envision the genus as a whole?

Applicant has argued, for example, that Merino et al. had described the "DAN family of BMP antagonists", which share the functional property of binding specifically to BMPs. In reply, it is again noted that the claims are directed to a genus of polypeptides that bind specifically to a bone morphogenetic protein-2 (BMP-2) so that BMP-2 receptor activation is prevented. The claims are not directed to structurally related family members, or to any polypeptides that share any degree of structural identity to one or another of the known polypeptides (e.g., noggin), which bind BMP-2 and block its binding to the BMP-2 receptor. Instead the claims are directed to structurally unrelated polypeptides, such as, for example, noggin and an antibody that binds BMP-2. Noggin has no apparent structural identity to such an antibody; and such an antibody appears to lack the structural features of noggin that confer its ability to bind BMP-2, and vice versa.

Applicant has asserted that as the claims have been amended to recite "a polypeptide that binds specifically to a bone morphogenetic protein-2 (BMP-2) so that BMP-2 receptor activation is prevented", the written description provision has been satisfied. In reply, as thoroughly explained in the preceding Office action, although the skilled artisan could potentially screen polypeptides to identify polypeptides having such functional features, the written description provision and the enablement provision set forth under 35 U.S.C. § 112, first paragraph, are separate and different requirements.

The description of a genus of substances to which the claims refer by the mere recitation of a functional property shared by its members does not suffice to adequately describe the genus as a whole. Although the polypeptides to which the claims refer are related in that each binds BMP-2 so that BMP-2 activation is prevented, the polypeptides that have been described (e.g., noggin, gremlin) are structurally different proteins, which have different, discrete physiologic functions; the disclosure of their common ability to bind BMP-2 does not describe their differing physiologic roles in the cell. Thus, the claims are directed to a genus of structurally and functionally disparate polypeptides, despite their common ability to bind BMP-2. Generalized language may not suffice to describe the invention, if it does not convey the detailed identify of the genus to which the claims refer, such that the skilled artisan could immediately envision, recognize or distinguish members of the genus and thereby distinguish infringing subject matter from non-infringing subject matter.

As a new matter necessitated by Applicant's amendment, it is noted the claims are directed to a method that results in the prevention of BMP-2 receptor "activation"; however, the specification does not describe what structural or functional changes in the BMP-2 receptor constitute or coincide with its activation. How does one determine when and if the BMP-2 receptor is activated? Does its phosphorylation constitute its activation? Does its oligomerization constitute its activation? Does a conformation shift in the oligomer constitute its activation? How does one measure its state of activation? Does it transduce a particular intracellular signal and/or activate another protein? Is its state of activation measured by assessing its ability to transduce a signal that causes a cell to undergo a particular phenotypic change? There is factual evidence of record that binding of BMP-2 to its receptor, or the inhibition of that interaction has contrasting effects upon the growth of certain tumor cells; is the BMP-2 receptor activated in one or both states of growth? How does one determine if its activation is prevented? It appears that the structural or functional changes in the BMP-2 receptor that define its state of activation, which are prevented from occurring by the polypeptide that binds BMP-2, have not been described, so as to reasonably convey to the skilled artisan that Applicant had possession of claimed invention at the time the application was filed.

Accordingly, although Applicant's arguments have been carefully considered, they have not been found persuasive to overcome this ground of rejection.

7. The rejection of claims 1, 6, and 17-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is maintained.

At pages 18-23 of the amendment filed August 10, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to

practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The claims are directed to a method for the treatment of lung cancer comprising administering to a patient a therapeutically effective amount of a polypeptide that binds specifically to BMP-2 *so that BMP-2 activation is prevented.* It is submitted that the amount of such a polypeptide that could reasonably be administered to a patient would not be reasonably expected to prevent BMP-2 receptor activation. The polypeptide to which the claims are directed binds BMP-2, the ligand of the receptor; it does not bind to the receptor. Perhaps binding of the polypeptide to a molecule of BMP-2 could prevent *that molecule* from binding a BMP-2 receptor, but because another BMP-2 molecule, which is not bound by the polypeptide, could still activate a receptor, prevention of BMP-2 receptor activation is not likely to be achieved by practicing the claimed invention.

Applicant has argued that many of references cited in the preceding Office action address the role of BMP-2 in colon, breast, prostate, gastric and brain cancer, but not its role in lung cancer. This fact does not diminish the relevance of the teachings of these references, however, in determining the state of the art, the predictability or unpredictability in the art, or in assessing the amount of experimentation that might be required before the skilled artisan could practice the claimed invention to treat lung cancer.

Applicant has argued that Tada et al. and Buckely et al. address the effects of BMP-2 on the growth of lung cancer cells, but only *in vitro* and not *in vivo*. Applicant has remarked, in contrast, Applicant's own publications teach the effects of BMP-2 on the growth of lung cancer cells in vivo using a mouse xenograft inoculated with human A549 lung cancer cells.

In response, it is again noted that the specification does not exemplify the use of the claimed invention; rather it shows that subcutaneous co-injection of agarose beads coated with recombinant mouse noggin and A549 lung cancer cells reduced the growth of the resulting tumor in nude mice. As explained in the preceding Office action, the claimed invention cannot be practiced in the "real world" by co-injecting the polypeptide

to which the claims refer (e.g., noggin) together with the tumor cells to be treated in a patient.

Langenfeld et al. (2004; of record) (i.e., the Applicant's own work published after the filing date of the instant application) discloses the results of the same or similar experiments as those described in the instant application. Although Langenfeld et al. teaches BMP-2 is overexpressed in the majority of patient-derived lung carcinomas tested, Langenfeld et al. discloses its role in cancer has not been established and while noggin appears to inhibit the growth of lung tumors in their experimental mouse model, the results of others' studies suggest inhibiting BMP-2 activity promotes tumor growth. Tada et al. (of record), for example, reports that using the same lung cancer cell line used by Langenfeld et al., the results of their studies indicate BMP-2 inhibits their growth under anchorage-dependent and -independent growth conditions, which suggests inhibiting its activity would not be clinically beneficial, but rather detrimental to the well being of the patient diagnosed with lung cancer.

Tada et al. is not the sole disclosure of such contrary results. Buckley et al. (of record) also discloses that BMP-2 suppresses the transformed phenotype of A549 lung cancer cells. Consistently, others of record (e.g., Hardwick et al., Haramis et al., Nishanian et al., Ghosh-Choudhury et al., Tomari et al., Nakamura et al., and Wen et al.) have reported that BMP-2 has a similar role in suppressing the growth of other types of cancers, including colon cancer, breast cancer, prostate cancer, stomach cancer, and brain cancer.

Thus, just as Langenfeld et al. (2002; of record) opines, it is apparent that the role of BMP-2 in cancer, including lung cancer has not yet been established. As a consequence, Langenfeld et al. states further studies are needed to define the role of BMP-2 in cancer.

Applicant has nevertheless argued that despite these opinions communicated by their post-filing date publications that the amount of guidance, direction and exemplification disclosed in the application would be sufficient to enable the skilled artisan to use the claimed invention without undue or unreasonable experimentation, since many of the studies referred to in the preceding Office action were not performed

using lung cancer cells, or were performed *in vitro*. Moreover, Applicant has asserted that because the specification shows reduced tumor growth in immunodeficient nude mouse model after co-injecting A549 human lung cancer cells and mouse noggin (i.e., the polypeptide of SEQ ID NO: 2), the skilled artisan could without undue or unreasonable experimentation clinically administer to a human patient diagnosed with lung cancer a therapeutically effective amount of any polypeptide that binds specifically to BMP-2 (e.g., human noggin, or the polypeptide of SEQ ID NO: 4) so as to prevent BMP-2 activation and thereby treat the lung cancer. However, the position of the Office is that such use of the claimed invention would not be reasonably enabled by the instant specification, as the skilled artisan could not do so without first establishing the role of BMP-2 in lung cancer, determine whether or not its inhibition would be clinically advantageous, and, if so, identifying and making suitable proteins that bind specifically to BMP-2 to prevent BMP-2 activation, such that the patient clinically benefits from the treatment. Moreover, as evidenced by Langenfeld et al., the amount of guidance, direction and exemplification is not sufficient to enable such use of the claimed invention.

Addressing Applicant's argument that the results of their studies performed *in vivo* outweigh the paradoxical and contrary results others' studies performed using the same cell line *in vitro*, it is noted that Gura and Bergers et al. address the common lack of extrapolation of the results of studies performed *in vivo* using mouse models to accurately and reliably predict the effects of the same treatments of human patients. As a consequence of such poor extrapolation, Gura teaches studies using mouse models often lead development of good mouse drugs rather than good human drugs, and Bergers et al. suggests careful evaluation of the effects of therapeutic agents in humans before transitioning from preclinical studies to clinical application.

Even so, Applicant has argued that the use of human A549 mouse xenografts for evaluating therapeutic efficacy of drugs for treating humans is well established; agreeably the model has been utilized, but its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation because of the poor extrapolation of the results to accurately and

reliably predict the effectiveness of treating humans with the same agent or regimen. Shul (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Shul discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Shul suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

To contrast that disclosed in the instant application, the specification teaches that inoculating mice with A549 tumor cells in the presence of mouse noggin reduced the growth of tumors at that site in nude mice.

The position of the Office that such exemplification is not sufficient to satisfy the requirement set forth under 35 U.S.C. § 112, first paragraph, is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Thus, Applicant's argument, given the proven efficacy of ZD1839 in phase I clinical trials, Sirotnak et al. have exemplified the utility of the A549 lung cancer xenograft model, in overt contrast to the reviewed and well-established inadequacy of such animal modeling, is anecdotal at best.

In further response, despite the finding disclosed in the instant application that co-injecting mouse noggin and A549 lung cancer cells slows or reduces the formation of tumors in immunocomprised mice, it is disturbing that contacting A549 lung cancer cell line with noggin *in vitro* promotes, rather than inhibits the growth of the cells. Why is it that mouse noggin acts to suppress the growth these cells in vitro but when injected into mice together with the cells apparently causes a reduction in their ability to form tumors? It is submitted that such a paradoxical finding is at odds with most, if not all other studies of potential therapeutic agents, since in general an agent that reduces the growth of tumor cells *in vitro* is expected to have the same effect *in vivo*. The finding that noggin has *opposite* effects upon the growth of A549 lung cancer cells *in vitro* and *in vivo* would not be expected. Again, it is because of such incongruous findings that Langenfeld et al. suggests the need for further experimentation before concluding that BMP-2 has a role in the progression, as opposed to the suppression of cancer.

Applicant has argued that a working example bearing a reasonable correlation to the entire scope of the claim should be considered sufficient to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph. However, the claimed invention has not been exemplified to any extent, since the specification merely shows reducing the growth of lung cancer cells by co-injecting tumor cells and mouse noggin into a mouse. The claims are directed to a method for treating lung cancer comprising administering to a patient a therapeutically effective amount of a polypeptide that binds specifically to BMP-2 so as to prevent BMP-2 receptor activation. As such the claims are directed to a method for treating *a pre-established tumor in humans*. Furthermore, the type and amount of exemplification disclosed are not reasonably commensurate in scope with the breadth of the claims, since the claims are directed to administering a member of *a genus of polypeptides*, including, in particular, the polypeptide of SEQ ID NO: 4, and yet the specification merely teaches injecting the polypeptide of SEQ ID NO: 2.

In addition, the specification provides an insufficient amount of guidance, direction and exemplification to enable the skilled artisan to make at least most of the members of the genus of polypeptides to which the claims are directed, namely polypeptides capable of specifically binding BMP-2 so that BMP-2 receptor activation is prevented. Again, the specification teaches human noggin (i.e., the polypeptide of SEQ ID NO: 4) and a few other proteins (e.g., gremlin), which were known to bind BMP-2, but, as explained in the "written description rejection:" above, the claims are directed to much broader genus of structurally and functionally disparate polypeptides. As explained in the preceding Office action, since the specification would not permit the skilled artisan to predict which polypeptides are capable of binding BMP-2 and preventing BMP-2 activation, the polypeptides to which the claims are directed can only be identified empirically.

Finally, as explained in the preceding Office action, the presumed utility of the claimed invention is largely based upon a disclosure in the specification of an observation that BMP-2 is overexpressed in lung cancer cells, as compared to normal lung cells; see, e.g., page 4, paragraph [0009]. However, by the amendment filed June 25, 2002, Applicant sought to amend the specification to indicate that because the primers used to amplify the nucleic acids encoding BMP-2 were potentially capable of amplifying both BMP-2 and BMP-4, which are highly homologous, the data presented therein cannot be definitively interpreted as showing amplification of BMP-2 in the absence of sequencing data. Then, at page 2 of that amendment, Applicant has remarked that subsequent sequencing of the RT-PCR products revealed amplification of BMP-4 rather than BMP-2. Since it seems that the underlying premise upon which the utility of claimed invention is asserted is amiss, it is questionable whether the pharmacologic inhibition of BMP-2 should be expected to produce a therapeutic effect in treating cancer.

In response to these remarks, in the paragraph bridging pages 21 and 22 of the amendment, Applicant has stated that the specification nevertheless discloses that the levels of BMP-2 are elevated in tumor samples derived from patients with lung cancer and it is upon this insight into the correlation that exists between lung tumor growth *in*

vivo and expression of BMP-2 that the asserted usefulness of practicing the claimed invention is based.

Still, it is not understood how an assertion that levels of BMP-2 are elevated in lung cancer is reasonably maintained when, as the amendment filed June 25, 2002 indicates, because the primers used to amplify the nucleic acids encoding BMP-2 were potentially capable of amplifying both BMP-2 and BMP-4, the data presented cannot be definitively interpreted as showing amplification of BMP-2 in the absence of sequencing data, which in the end revealed amplification of BMP-4 rather than BMP-2.

In conclusion, although Applicant's arguments have been carefully considered, upon equally careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there is a preponderance of factual evidence of record that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Double Patenting

8. The provisional rejection of claims 1, 18, and 19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 14 of copending Application No. 10/692,824. Although the conflicting claims are not identical, they are not patentably distinct from each other for reasons set forth in section 20 of the preceding Office action mailed April 25, 2005. In addition, because copending claim 1 has since been amended to recite the BMP-2 inhibitor comprises noggin, it is noted that the specification of the copending application defines "noggin" as specifically denoting human noggin of SEQ ID NO: 4; see, e.g., original claim 12 and paragraph [0074].

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

At page 23 of the amendment filed August 10, 2005 Applicant has requested that this issue be held in abeyance until allowable subject matter has been identified in the copending application.

Applicant's request is acknowledged.

New Ground of Rejection

9. Claims 1, 6, and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

As presently amended, claim 1 recites, "so that BMP-2 receptor activation is prevented".

At page 13 of the amendment filed August 10, 2005 Applicant has stated that no new matter has been added by the amendment. At page 18, paragraph 2, of the amendment Applicant has stated that support for the changes to claim 1 are found in the specification at page 17, lines 10-17, and in the paragraph bridging pages 35 and 36.

To the contrary, however, it does not appear that the specification, including the claims, as originally filed, provides proper and sufficient written support for the recitation in claim 1 that administering to a patient a therapeutically effective amount of a polypeptide that binds specifically to BMP-2 receptor activation is prevented.

At page 17 the specification describes noggin as an antagonist of BMP-2 activity; this disclosure does not appear to support the recitation, "so that BMP-2 receptor activation is prevented".

In paragraph [00101], which bridges pages 35 and 36, the specification discloses: "Noggin, a natural inhibitor of BMP-2, is a secreted protein that binds BMP-2 and BMP-4, thereby preventing their activation of the BMP receptors" (underlining

added for emphasis). This disclosure appears to describe noggin as capable of binding BMP-2 and moreover, it appears to describe BMP-2 molecules, which are bound by noggin, as incapable of activating BMP-2 receptor. However, this disclosure is not reasonably commensurate in scope with the language of the claims, as this disclosure strictly refers to noggin, rather than to the genus of polypeptides to which the claims are directed, which bind BMP-2 so as to entirely prevent BMP-2 receptor activation. Accordingly, this disclosure is not deemed to provide proper and sufficient written support for the language of the claim 1.

Furthermore, as subtle a difference as it may well be, this disclosure does not appear to adequately describe administering to a patient a therapeutically effective amount of a polypeptide that binds specifically to a BMP-2 *so that BMP-2 receptor activation is prevented*. Since only neutralized BMP-2 molecules, which are bound by noggin, are incapable of binding the receptor and, in turn, activating the receptor; active BMP-2 molecules that are not bound by noggin and any other ligands of the receptor, known or yet to be discovered, are still capable of binding and activating the receptor. Thus, the claims are directed to a method resulting in global and complete prevention of BMP-2 activation, whereas the specification appears to merely provide support for preventing BMP-2 receptor activation by those BMP-2 molecules that are bound by noggin. In other words, the language of the claim and the language of the disclosure are not of reasonably equal scope. For this reason, claim 6 is included in this rejection, even though the polypeptide that binds specifically to BMP-2 is human noggin of SEQ ID NO: 4.

This issue might be remedied if claim 1 were amended to recite, for example, "administering to a patient with lung cancer a therapeutically effective amount of the polypeptide of SEQ ID NO: 4 to antagonize binding of BMP-2 to its receptor". Otherwise, this issue might be remedied if Applicant were to point to specific disclosure in the specification, including the claims, as originally filed, which are believed to provide the necessary written support.

Conclusion

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
October 24, 2005